

# *Marijuana Science Update*



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# NIDA **CANNABIS** SCIENCE RESEARCH AREAS

- **EPIDEMIOLOGY:** National and Local Surveys, including co-occurring MI and SUD
- **PREVENTION:** ABCD; SBI; Implementation of evidence based programs; **Effective messaging and programs for “legal cannabis”**
- **NEUROSCIENCE:**
  - Endocannabinoid System
  - Impact of exposure/use/addiction on brain structure and function; cognition; motivation; affect; fetal development
- **TREATMENT of Cannabis Use Disorder:**
  - Medications, Devices (e.g., TMS), psychosocial (behavioral)
  - Relapse prevention and withdrawal treatment
- **POLICY:** ***Developing a research agenda now***
  - Identify greatest needs: e.g., better measures, including impairment; social consequences; regulatory models

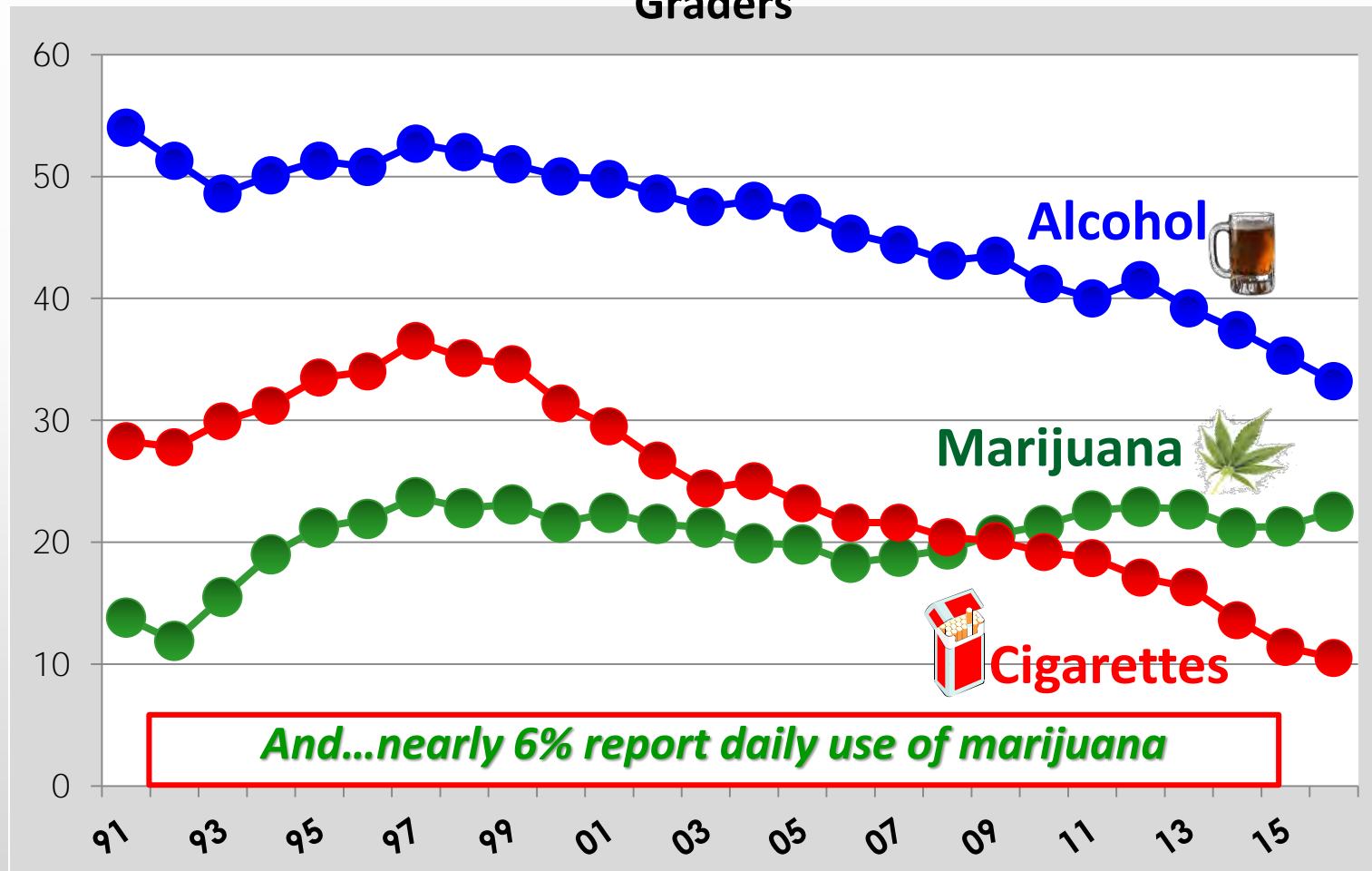


# CANNABIS: MOST COMMONLY USED "ILLICIT" DRUG IN THE U.S.

- Over **22 million** Americans 12 and older were past month marijuana users.
- Approximately **4.0 million** Americans met criteria for cannabis use disorders in 2015.
- An estimated **2.6 million** Americans used it for the first time; **1.2 million** were between the ages of 12 and 17.

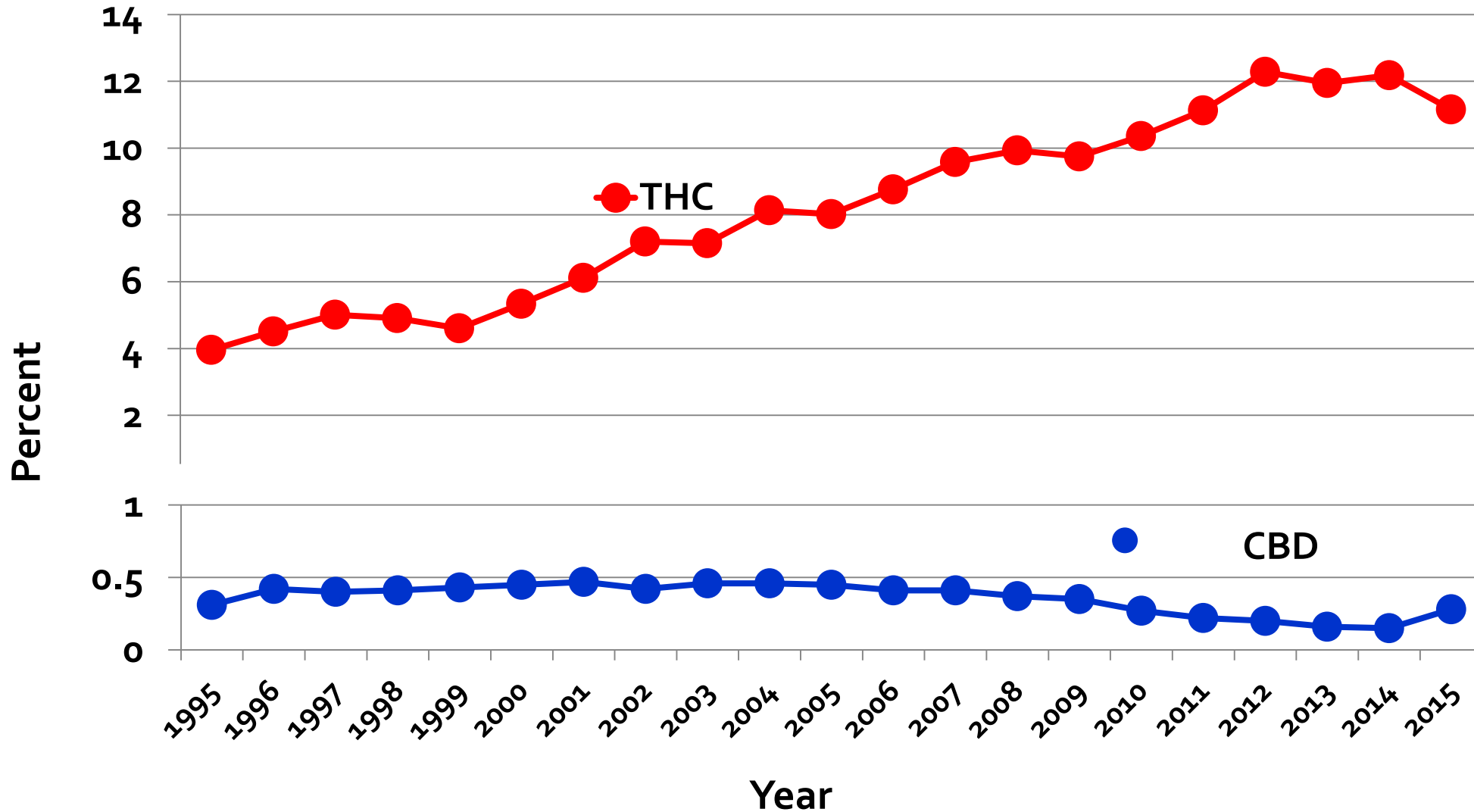
Source: 2016 National Survey on Drug Use and Health, SAMHSA

Past Month Use of Cigarettes, **Marijuana**, and Alcohol in 12<sup>th</sup> Graders



Source: University of Michigan, 2016 Monitoring the Future Study

# Marijuana Potency (% $\Delta$ -9 THC) Tripled in Past 20 Years



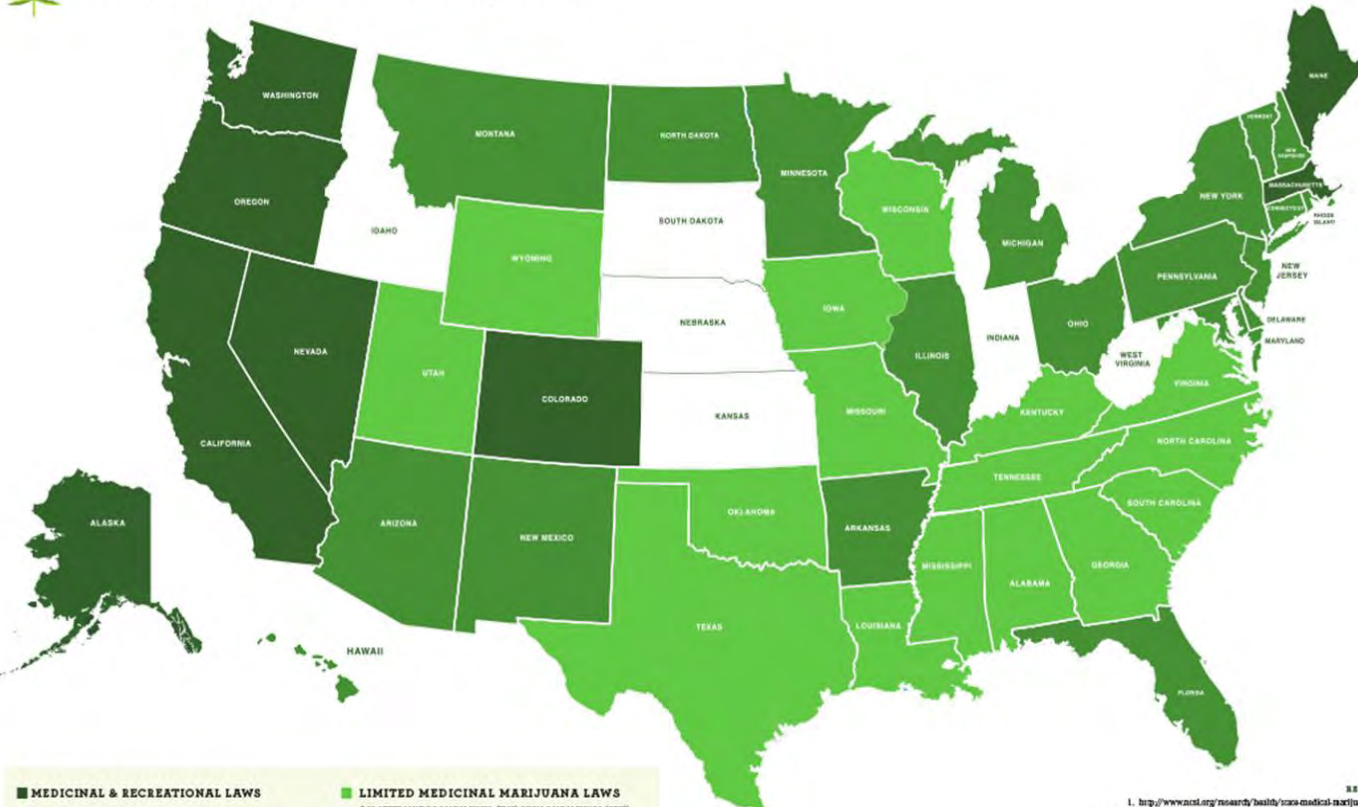


# Variation in Legal Status of Marijuana

# Increasing Regular Use of Marijuana, by Adults

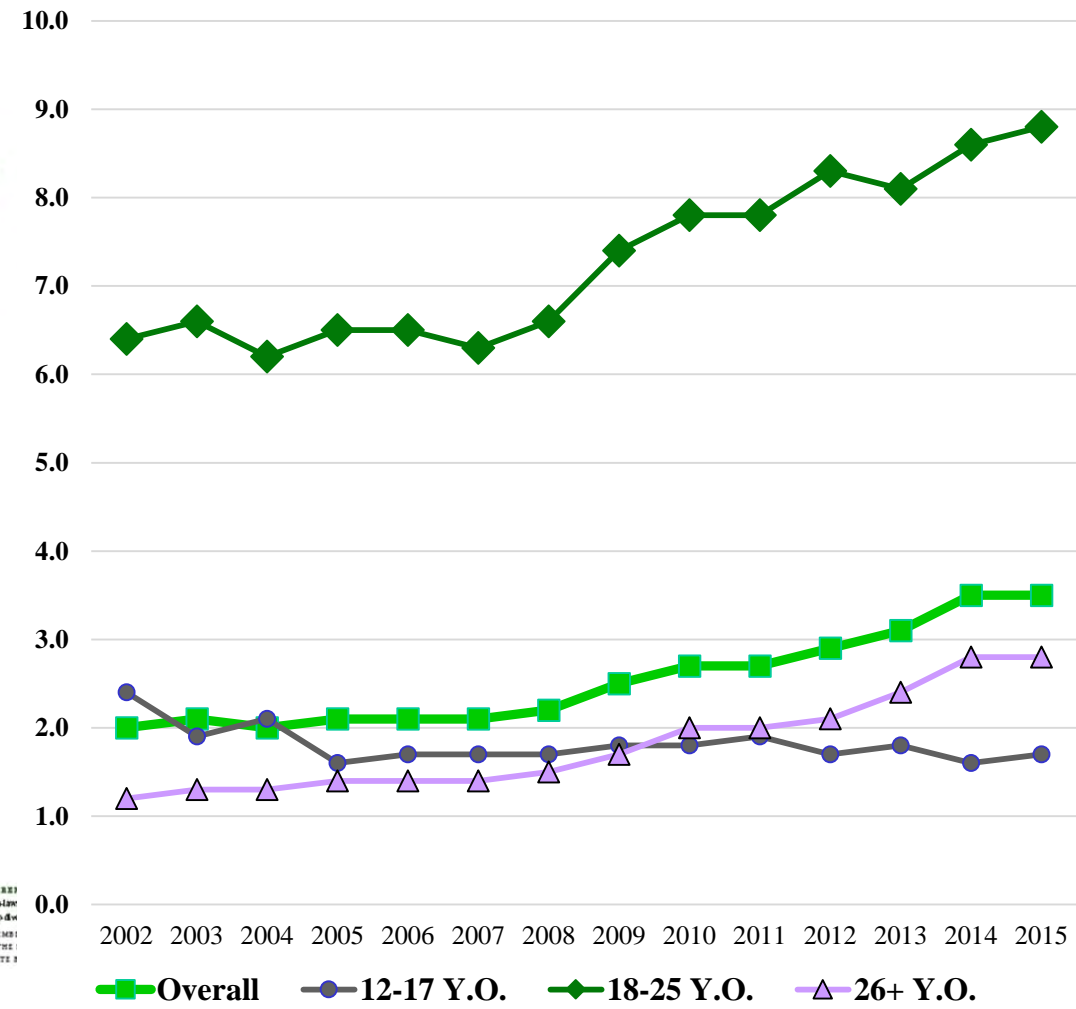


Marijuana Laws Differ State by State



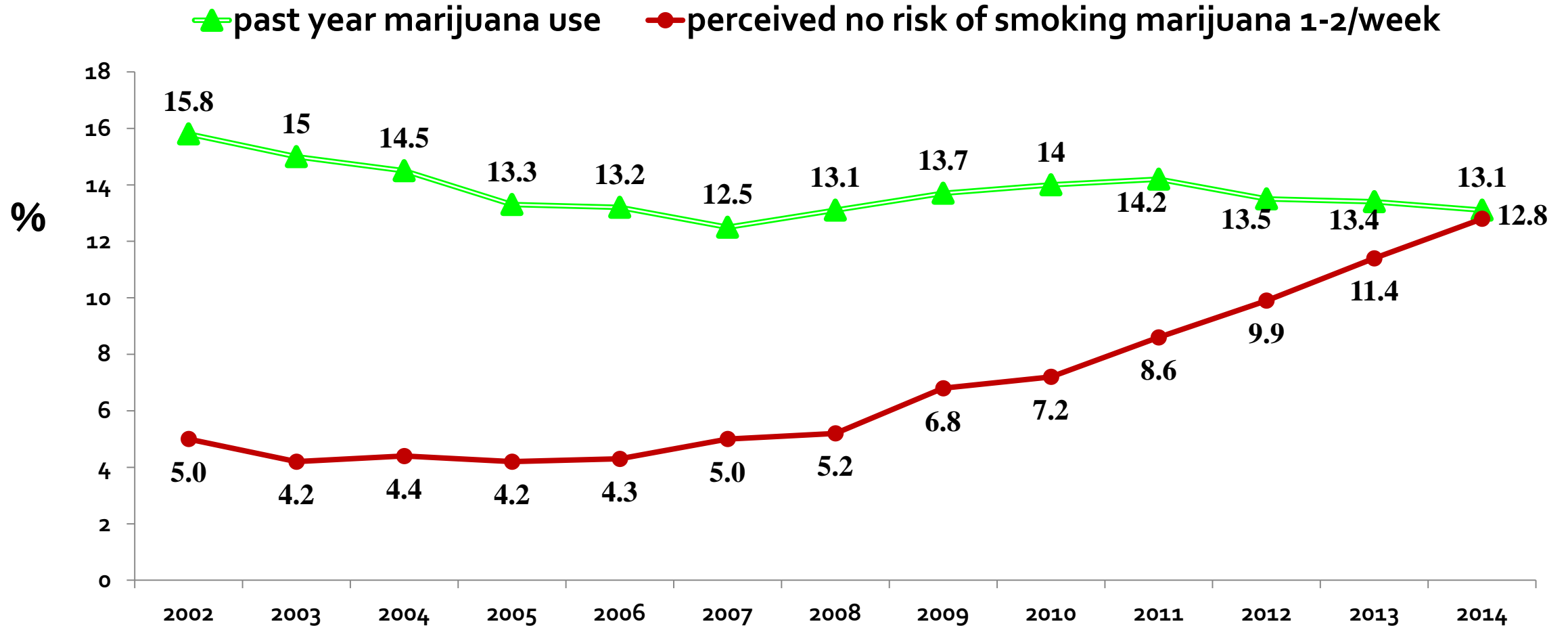
■ MEDICINAL & RECREATIONAL LAWS  
■ COMPREHENSIVE MEDICAL MARIJUANA LAWS  
■ LIMITED MEDICINAL MARIJUANA LAWS (LOW TETRAHYDROCANNABINOL (THC), HIGH CANNABIDIOL (CBD))  
■ NO MARIJUANA ACCESS

1. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3421212/>  
 2. <http://www.aicd.org/health/issue/marijuana-disp.html>  
 STATES LAWS STATUS CURRENT AS OF DECEMBER 2014  
 LOCAL GOVERNMENT WEBSITES HAVE ADDITIONAL INFORMATION ON THE REGARDING MEDICINAL AND RECREATIONAL MARIJUANA ON A STATE-BY-STATE BASIS



SAMHSA, National Survey on Drug Use and Health, 2015.

# Declining Marijuana Use in 12-17 year olds Despite Declining Risk Perception: *Associated with Tobacco Use Declines?*



Han, Compton, et al. *Journal of Clinical Psychiatry*, 2017

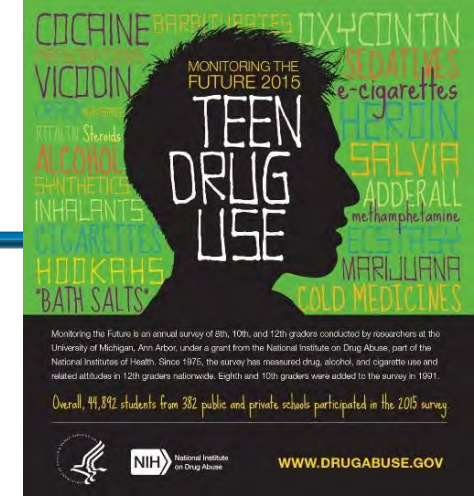
# MJ Patterns and Trends

## What We Know:

- Use among youth (12-17) has not increased in recent years despite decreased perception of risk
- Use has increased in older teens and adults
- Current users use more often (daily, nearly daily) than in 2002
- Potency is increasing; plant components are changing
- Cannabis is being administered through different routes

## What We Need to Know:

- Need improved measures of frequency, dosage, patterns of use
- Persuasive Messaging (especially for youth) to counter the trend of decreasing harm perception
- Greater knowledge of the impact of changing potency, constituents, and alternative routes of administration
- Regional differences based on changing laws, policies, and social norms
- Use of other substances: complementarity vs. substitution



# CANNABIS' ACUTE EFFECTS

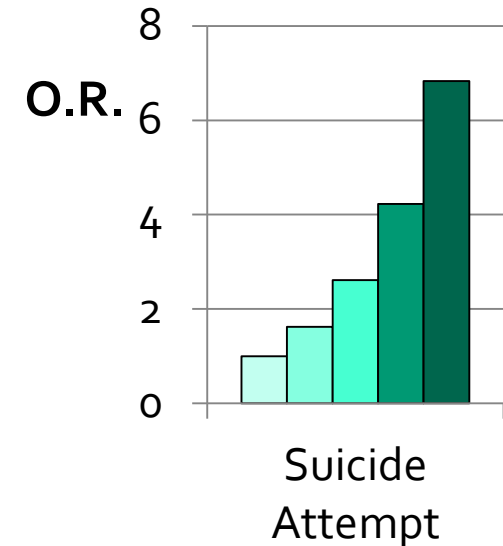
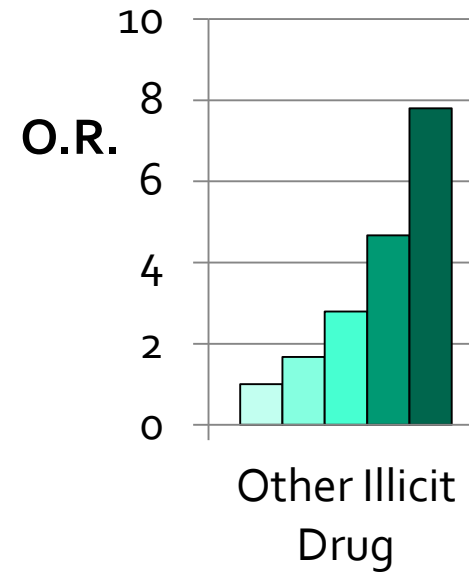
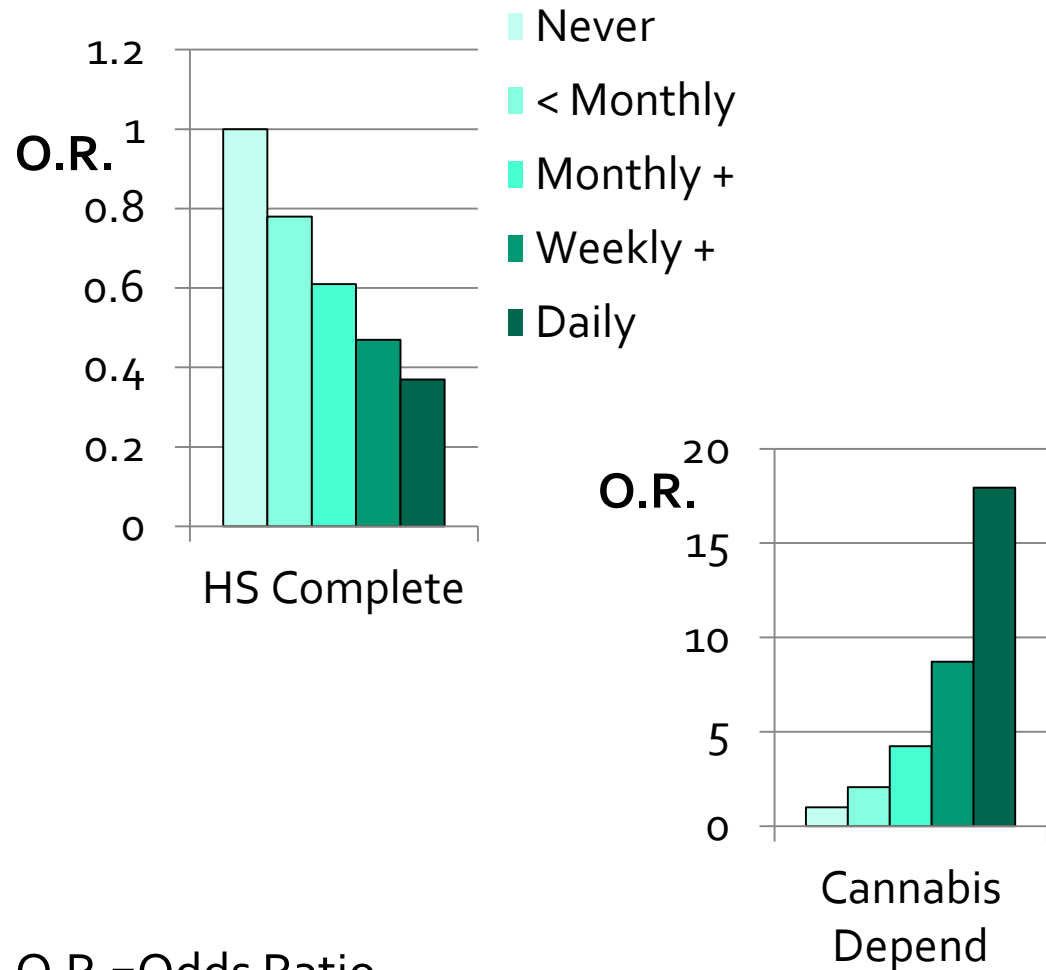
## (INTOXICATION PHASE)



- Euphoria
- Calmness
- Appetite stimulation
- Altered perception of time
- Heightened sensation
- Impairs coordination and balance
- Increased heart rate: 20 - 100%
- Orthostatic (postural) hypotension
- **Increased risk of accidents (~2 fold), higher when combined with alcohol**
- Impaired short-term memory
  - Difficulty with complex tasks
  - Difficulty learning
- Executive Function
  - Impaired decision-making
  - Increased risky behavior – STDs, HIV?
- Mood (especially after high doses or Edibles)
  - **Anxiety – panic attacks**
  - **Psychosis – paranoia**

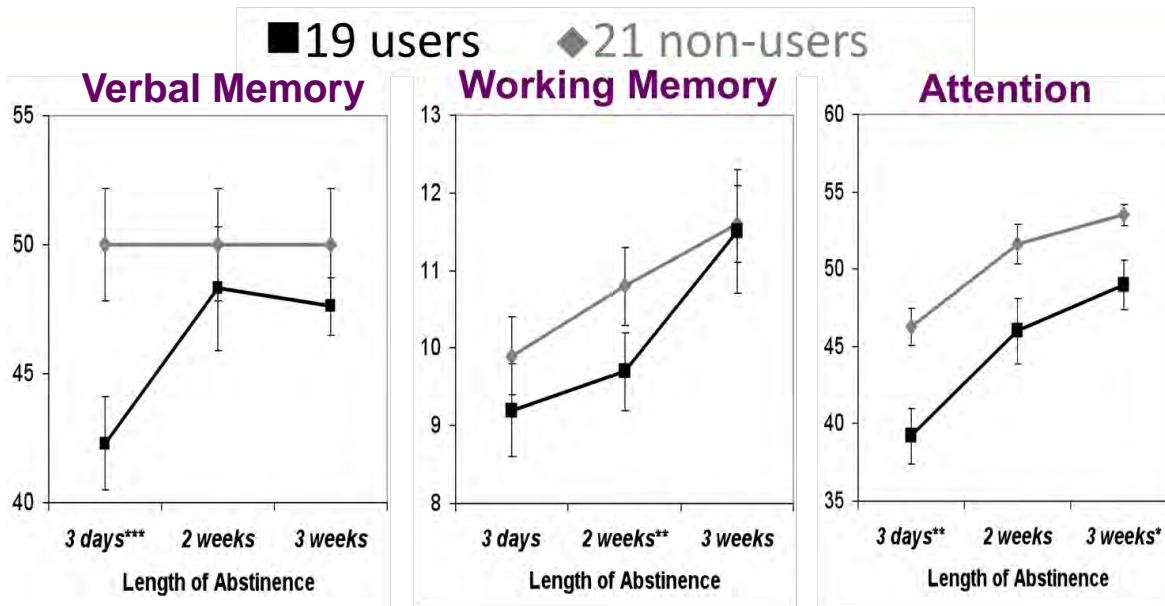


# More Teenage Use of Cannabis Associated with Worse Longer Term Outcomes in 20's (3 large Australia/New Zealand Studies)

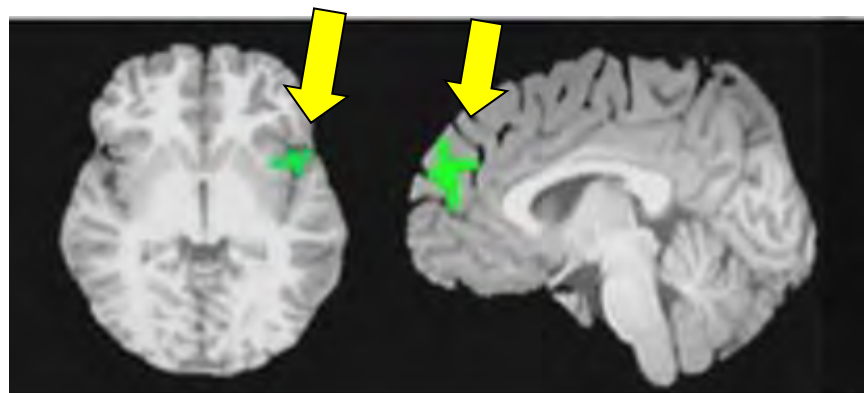
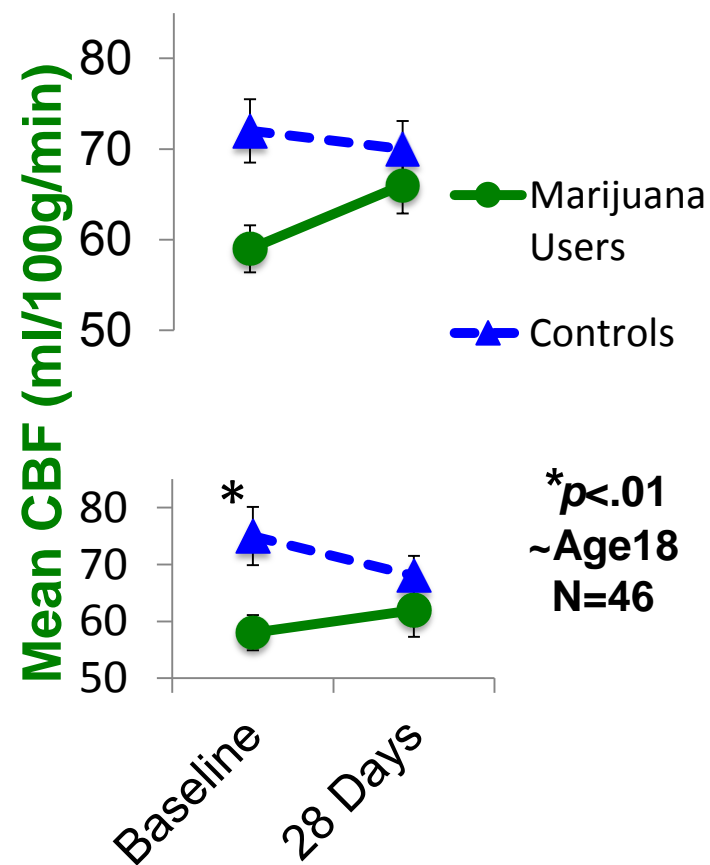


O.R.=Odds Ratio

# Recovery of Cognition and CBF with Abstinence



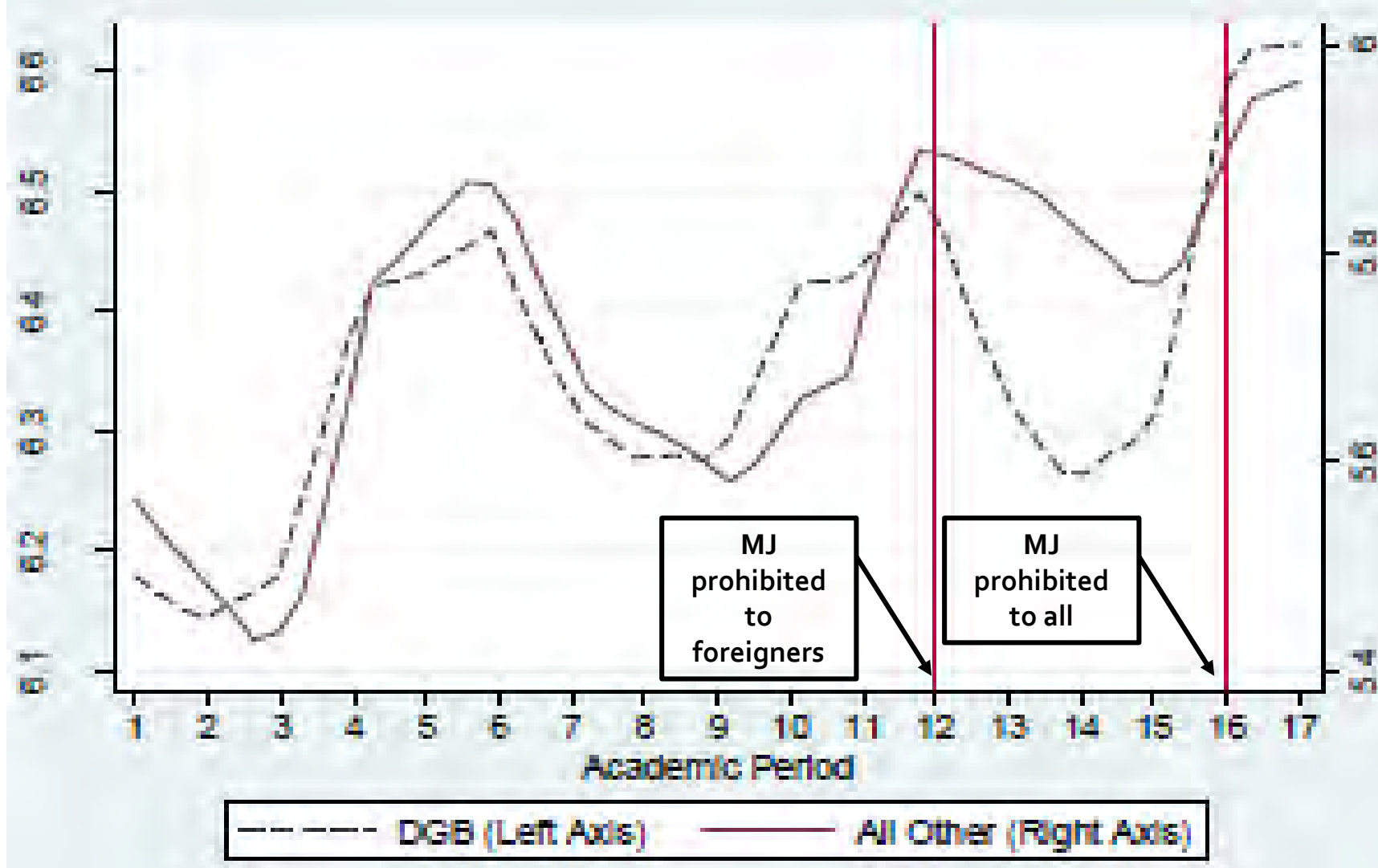
## Brain blood flow after 28 days monitored abstinence



Left Insula

Medial Frontal Gyrus

# When MJ Sales Were Restricted in The Netherlands, University Grades Improved



# Cannabinoid Receptors Are Located Throughout the Brain



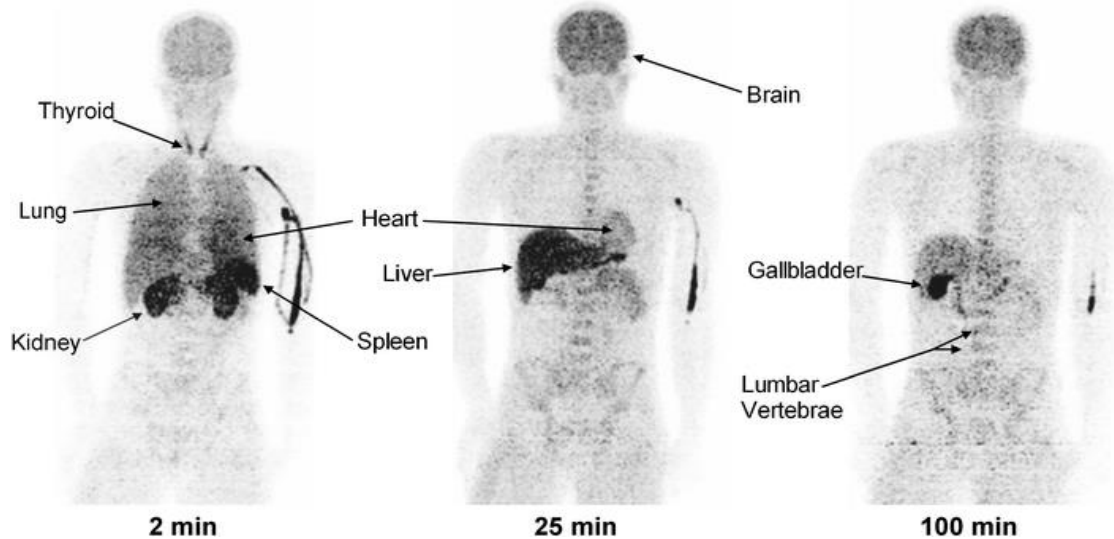
## Regulation of:

- Brain Development
- Memory and Cognition
- Movement Coordination
- Pain Regulation & Analgesia
- Immunological Function
- Appetite
- Motivational Systems & Reward



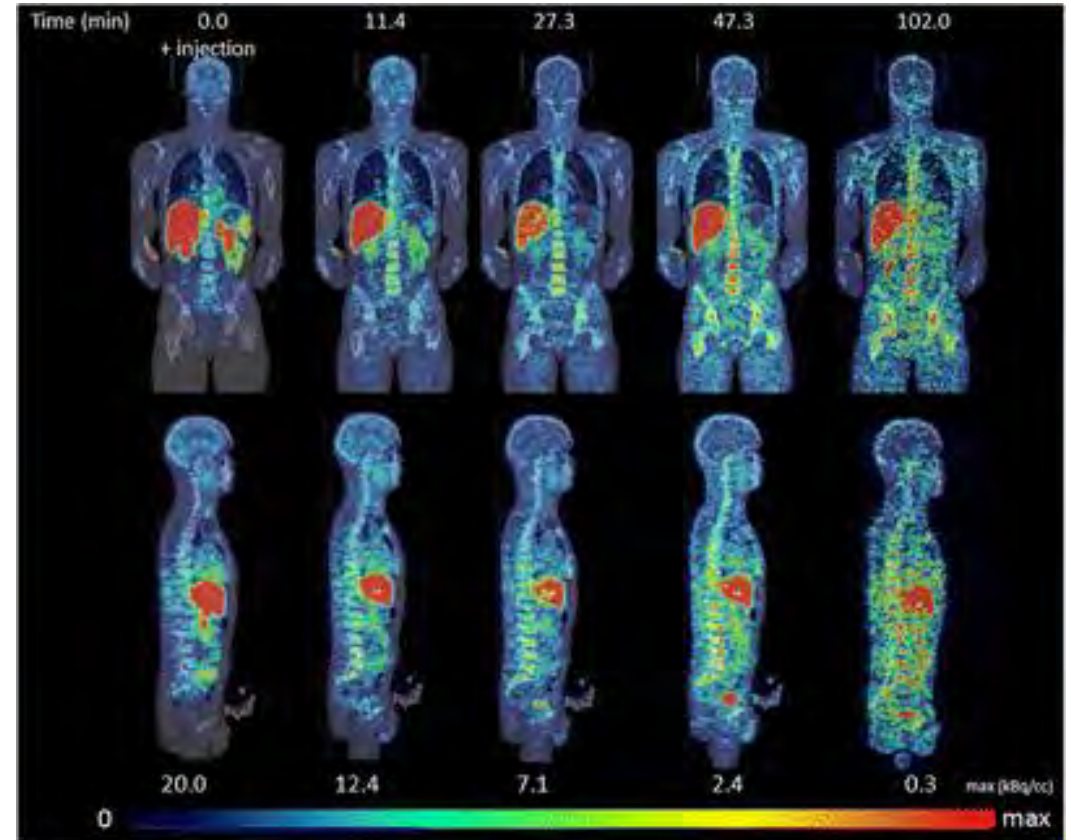
# Cannabinoid Receptors Are Also Located Throughout the Body

Whole Body Distribution of CB<sub>1</sub> Receptors (2, 25, and 100 min after injection of <sup>11</sup>C-MePPEP)



Terry et al., *Eur J Nucl Med Mol Imaging*. 2010

PET images of [<sup>11</sup>C]-NE<sub>40</sub> (CB<sub>2</sub>R radioligand)

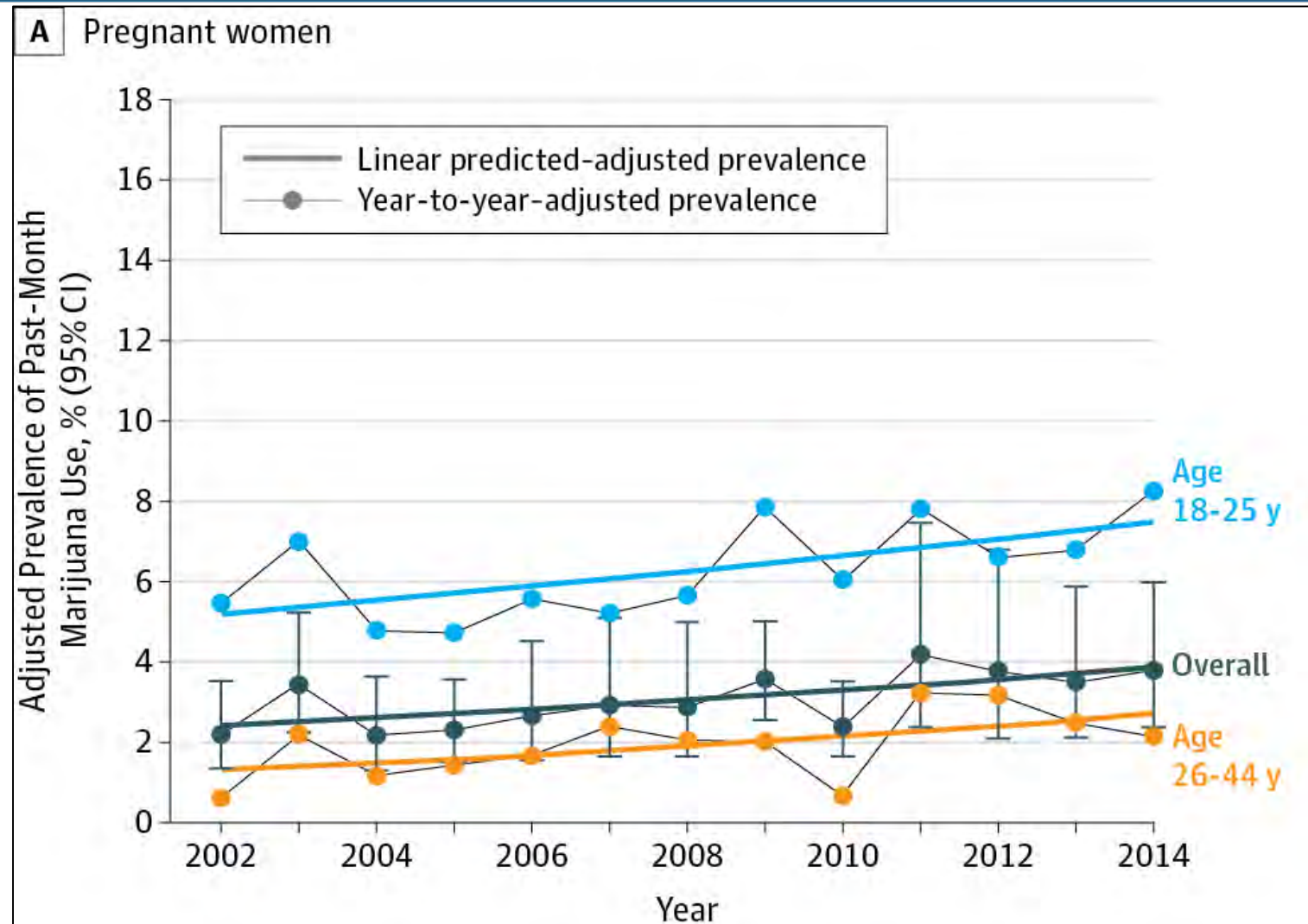


Ahmad et al., *Mol Imaging Biol*. 2013 A



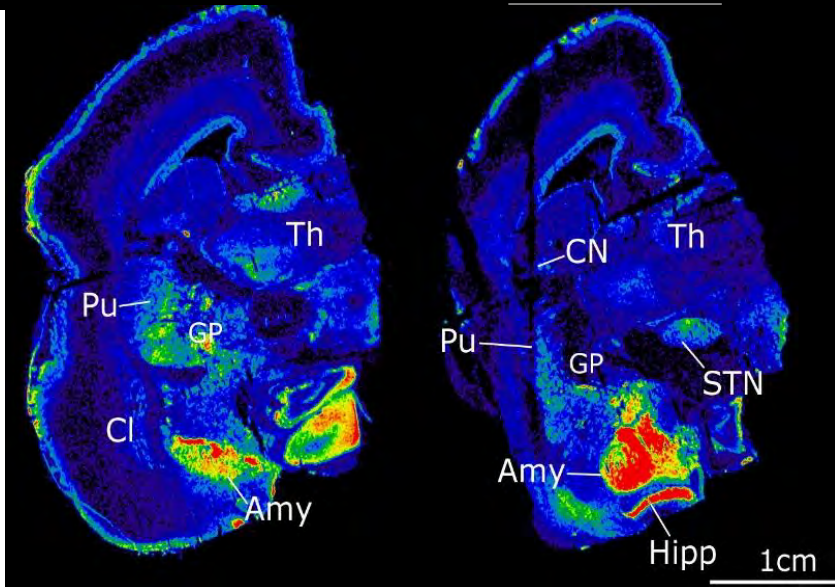
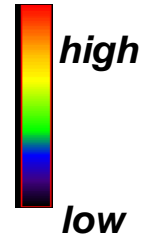
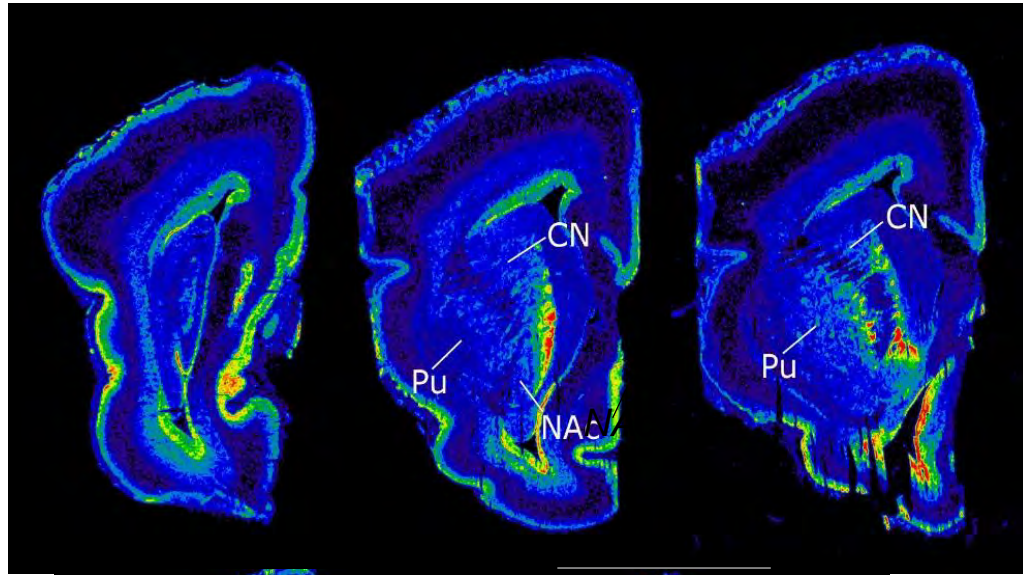
# *Cannabis Use During Pregnancy* is increasing

Trends in  
Prevalence of  
Cannabis Use in  
Pregnant Women,  
2002-2014-  
NSDUH



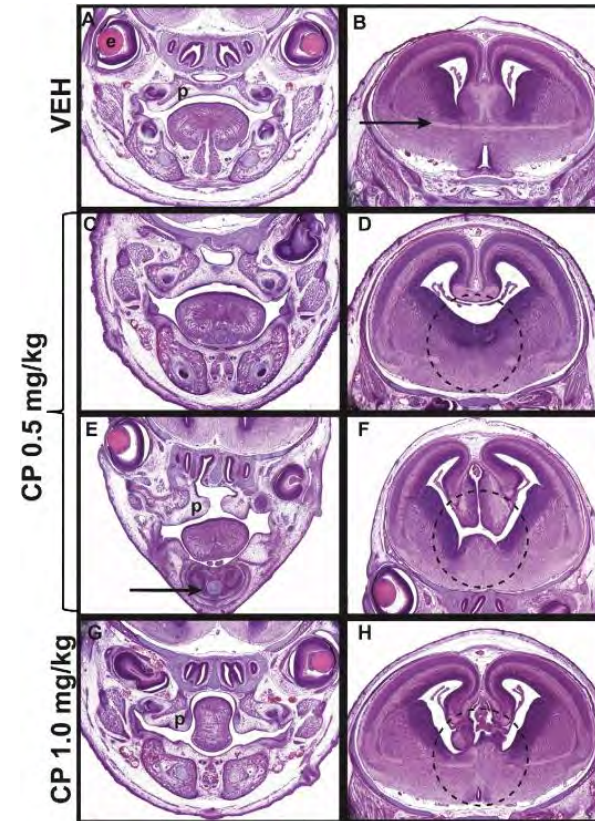
Source: Brown et al., 2017

# Cannabinoid (CB<sub>1</sub>) Receptors are Expressed in Human Fetal Brain



Wang et al, Neuroscience, 2003

# A Powerful Cannabinoid Agonist (CP-55,940) Causes Brain Malformations in Fetal Mice



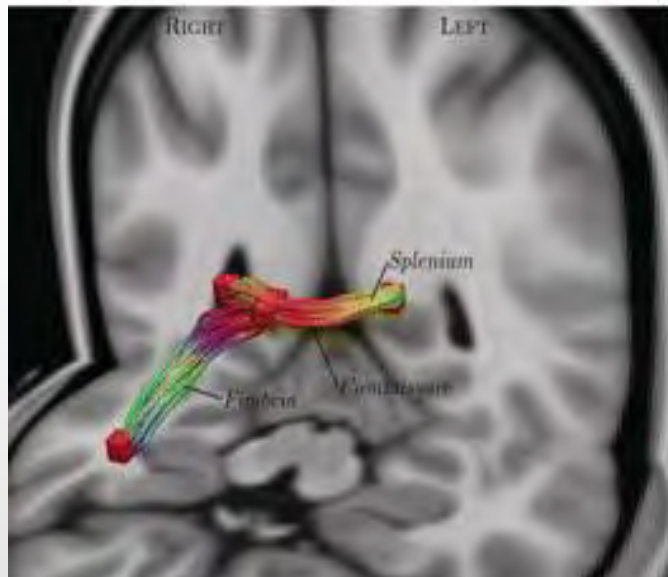
CP 55,940-treated fetal mice showing abnormalities of the brain, eyes, palate, and mandible. CP 55,940 is 45-times more potent than THC.

Marcoita et al., Neurotox Teratology, 2015.

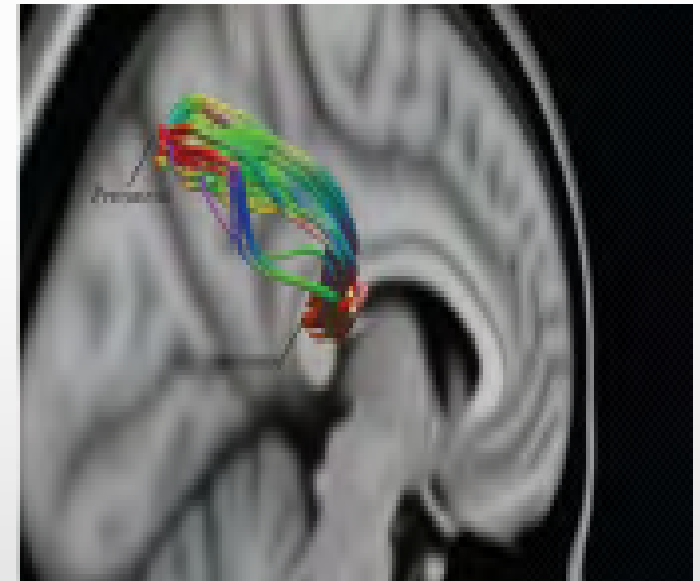
# MULTIPLE STUDIES SHOW **ALTERED BRAIN STRUCTURE AND FUNCTION** IN YOUTH WHO REGULARLY USE CANNABIS

Early (<18y) Cannabis Use Decreases Axonal Fiber Connectivity

Precuneus to splenium



Fimbria of hippocampus, hippocampal Commissure, and splenium

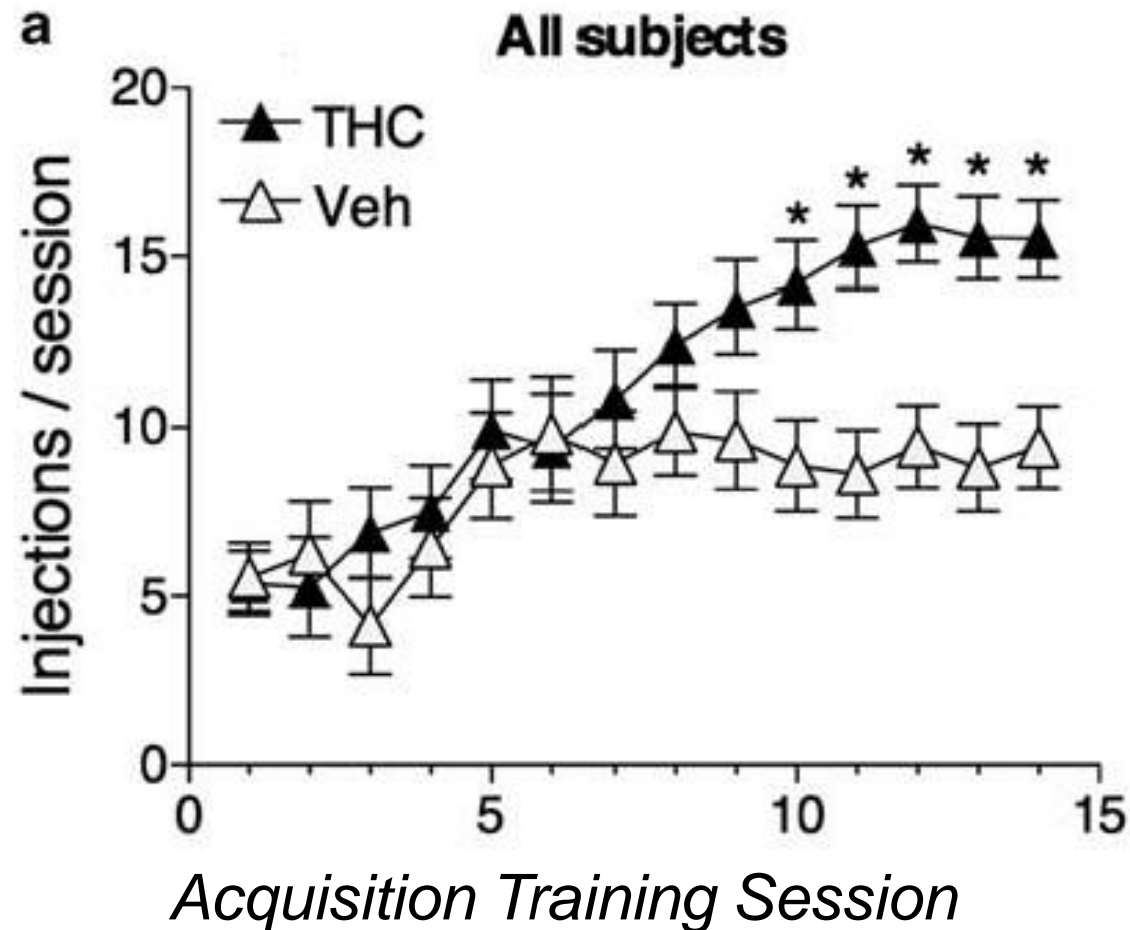


Axonal paths with reduced connectivity (measured with diffusion-weighted MRI) in cannabis users (n=59) than in controls (N=33).



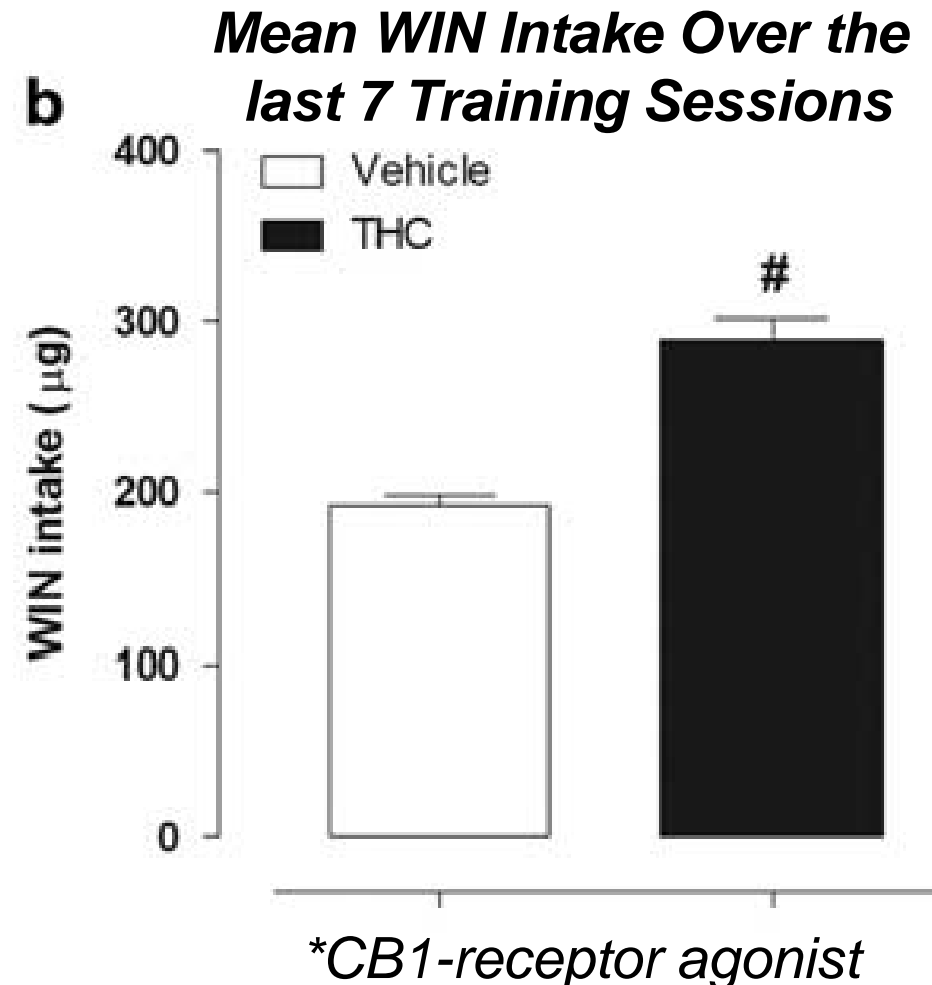
# Use of Rewarding Substances During Adolescence Primes the Reward System, Increasing Risk for Drug Abuse

**THC Exposure Alters  
Nicotine Self-Administration (SA)**



Panlilio LV et al., *Neuropsychopharmacology* 2013; 38:1198-1208.

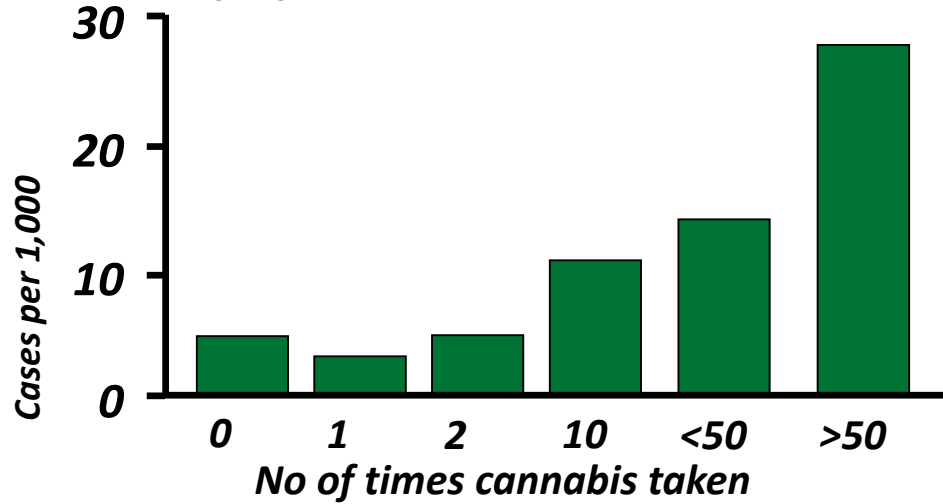
**Adolescent  $\Delta^9$ -THC Exposure Alters  
WIN55,212-2\* SA in Adult Rats**



Scherma M et al., *Neuropsychopharmacology* 2016; 41:1416-1426.

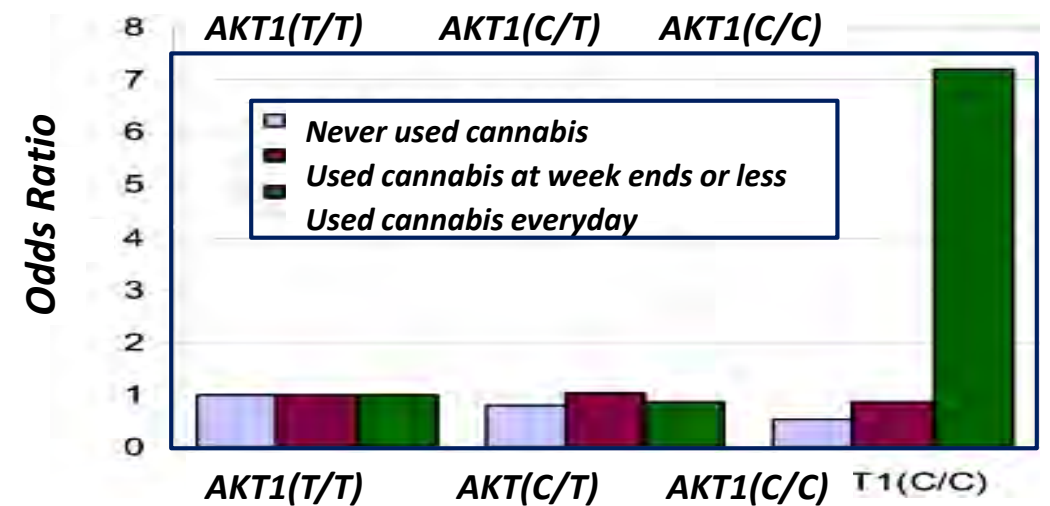
# Heavy Cannabis Use Increases Risk for Schizophrenia in People with a Genetic Predisposition

Study of Swedish Conscripts (n=45570)



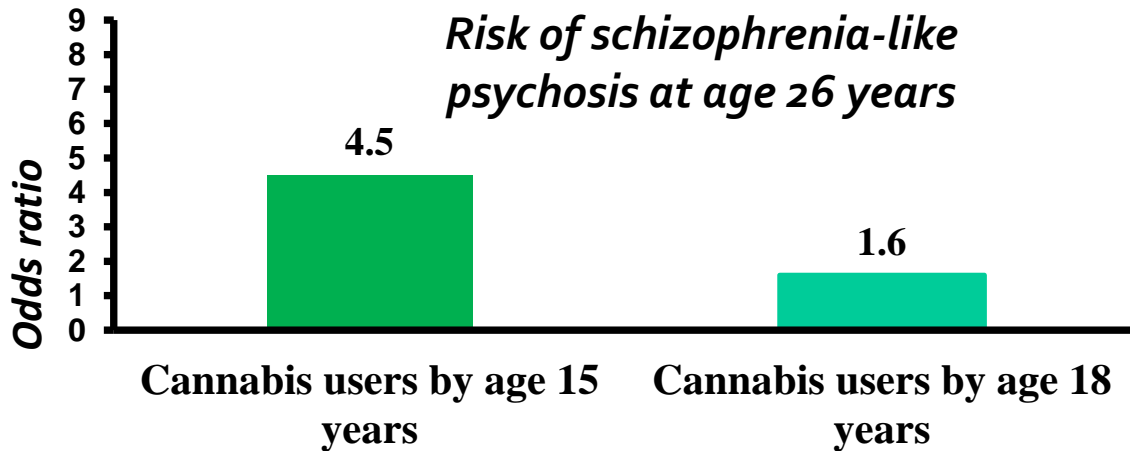
Andréasson et al Lancet, 1987.

Risk Conferred by AKT1 Gene



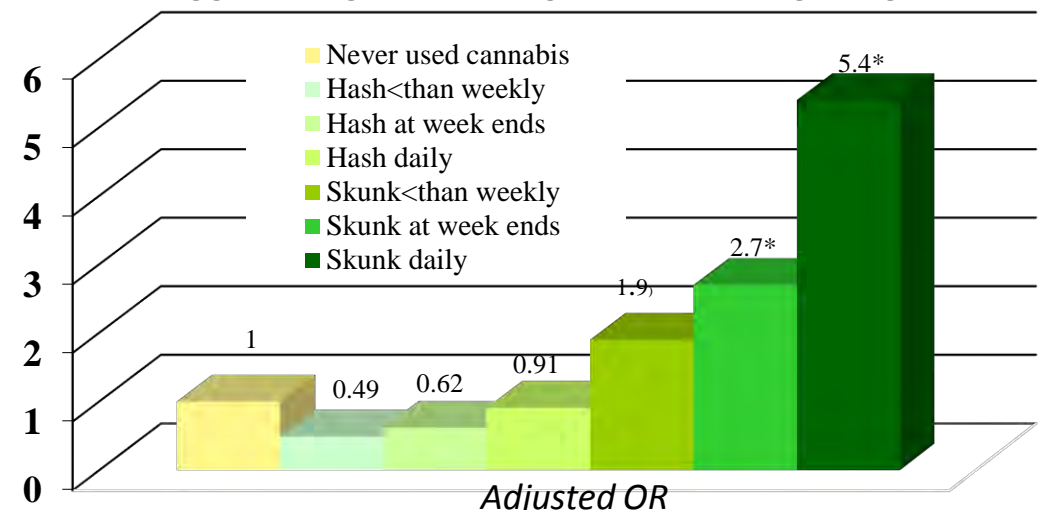
Di Forti et al., Biological Psychiatry, 2012.

Prospective Dunedin study (n=1037)



Arseneault et al BMJ 2002

Effect of Potency on Risk of Psychosis



Di Forti M et al., The Lancet, 2015.



# Other Marijuana-related Health Concerns

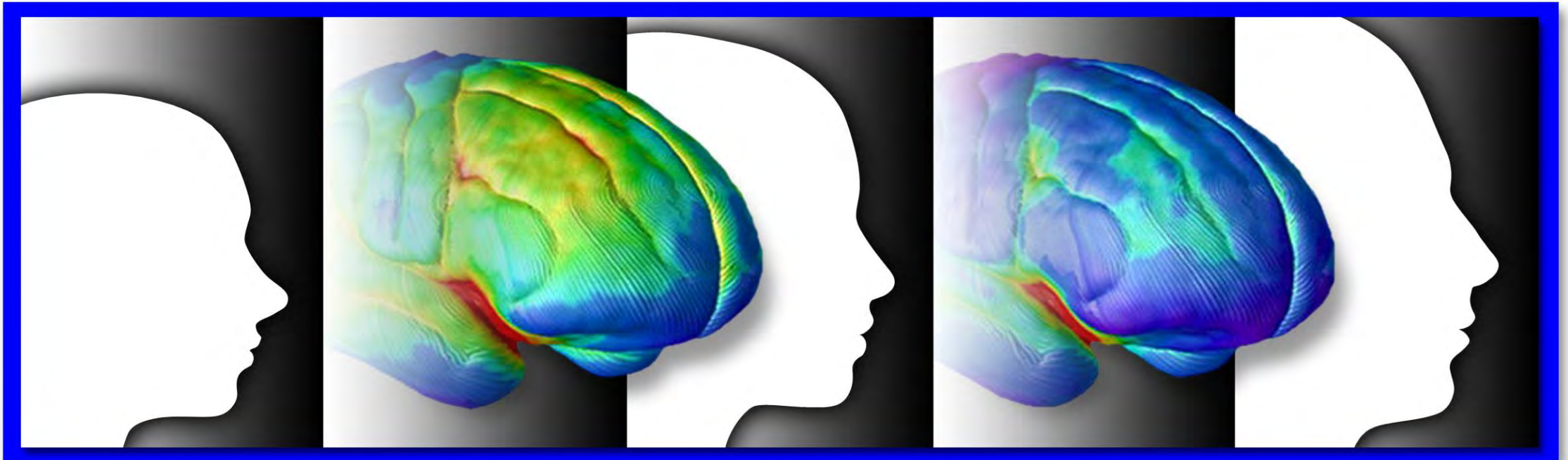
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- **Addiction potential (increased with heavy use and adolescent onset)**
  - ***Need for better treatments of Cannabis Use Disorder***
- **Second hand exposure**

# ***Adolescent Brain and Cognitive Development (ABCD) Study*** ***NIDA, NIAAA, NCI, NICHD, NIMH, NIMHD, OBSSR, NINDS***

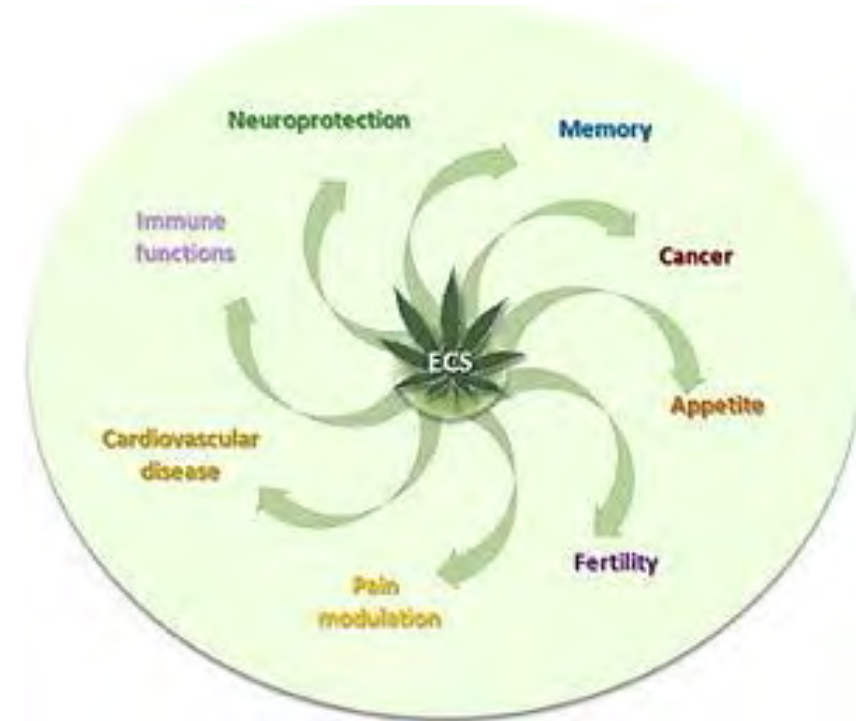
***Ten year longitudinal study 10,000 children from 10 to 20 years to assess effects of drugs (including nicotine, and, marijuana and alcohol) on individual brain development trajectories and functional outcomes***



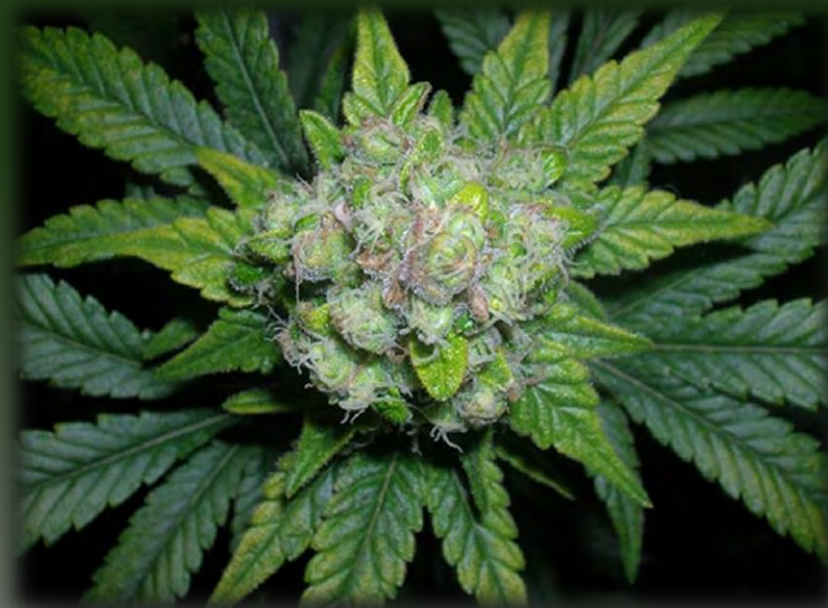
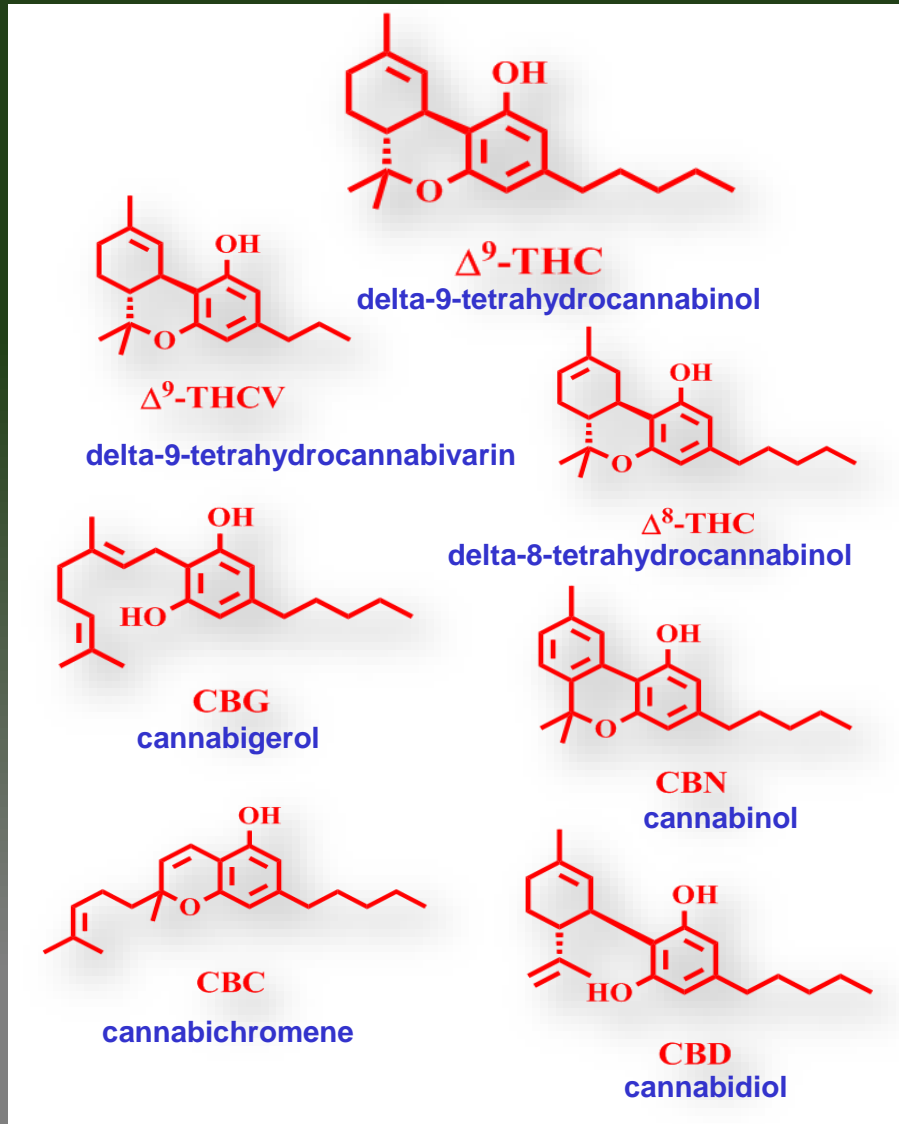
## **Adolescent Brain Cognitive Development**

# Exploiting the Cannabinoid System for Therapeutic Purposes

- Exogenous compounds
  - Phytocannabinoids
    - THC, CBD, combinations
  - Synthetic cannabinoids
    - Dronabinol
- Endogenous manipulation
  - FAAH inhibitors
  - MAGL inhibitors
  - Allosteric modulators
- Receptor targets
  - CB<sub>1</sub>, CB<sub>2</sub>, TRPV<sub>1</sub>, PPAR, 5-HT, peripheral, others...



# Marijuana contains ~100 cannabinoids plus other chemicals in varying concentrations



# Enzyme Inhibitors (e.g., AEA degradation)

Indirect enhancers of CB activity—more selective, less side effects  
What have we learned?

**FAAH inhibitors**

**ECB**

**Reduce anxiety-like behaviors**

**Reduce depression-like behaviors**

**Enhance social behavior in ASD models**

**Reduce nicotine addiction**

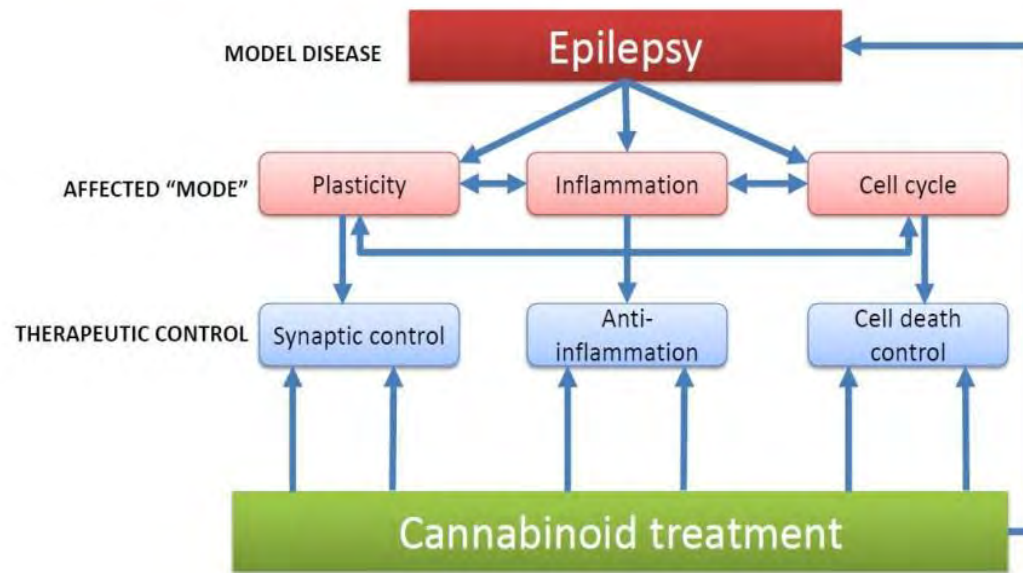
**May be effective for cannabis use disorder**

**Very mild side effect profile  
in animals and humans**



# Cannabidiol in Treatment Resistant Dravet Syndrome (Epilepsy)

Cannabinoids are effective in models of epilepsy GW



Devinsky O et al., 2015 Annual Meeting of the American Epilepsy Society, and *New England Journal of Medicine* 2017;376:2011-2020

Fig. 1: Median % Reduction in Total Seizures

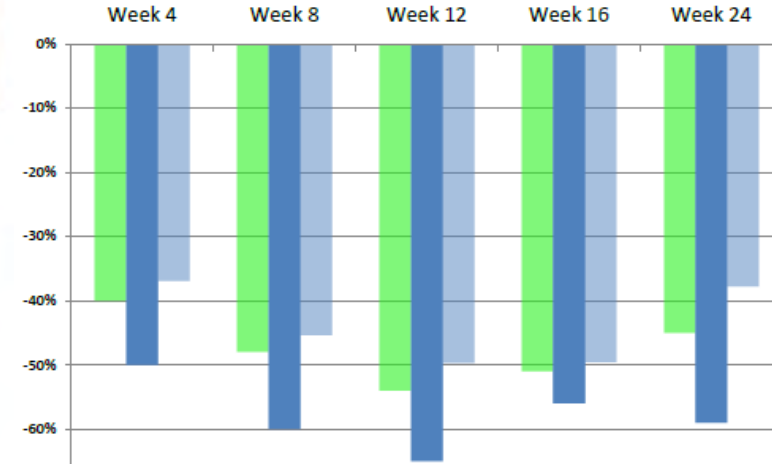
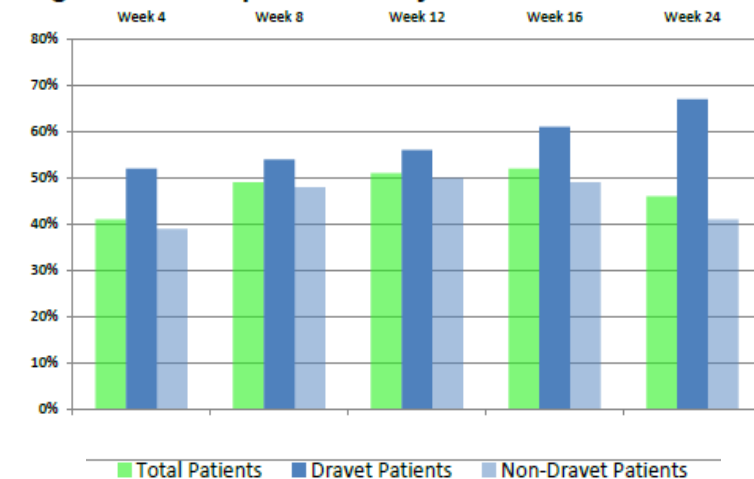


Fig. 2. 50% Responder Analysis – Total Seizures



# RECENT META-ANALYSES SUPPORT THE USE OF CANNABINOIDS FOR CHRONIC NEUROPATHIC NON CANCER PAIN, BUT.....

➤ Studies generally short, small, with modest effect sizes.

J Neuroimmune Pharmacol (2015) 10:293–301  
DOI 10.1007/s11481-015-9600-6

INVITED REVIEW

## Cannabinoids for the Treatment of Chronic Non-Cancer Pain: An Updated Systematic Review of Randomized Controlled Trials

M. E. Lynch<sup>1,3</sup> · Mark A. Ware<sup>2</sup>

Received: 29 January 2015 / Accepted: 5 March 2015 / Published online: 22 March 2015  
© Springer Science+Business Media New York 2015

**Abstract** An updated systematic review of randomized controlled trials examining cannabinoids in the treatment of chronic non-cancer pain was conducted according to PRISMA guidelines for systematic reviews reporting on health care outcomes. Eleven trials published since our last review met inclusion criteria. The quality of the trials was excellent. Seven of the trials demonstrated a significant analgesic effect. Several trials also demonstrated improvement in secondary outcomes (e.g., sleep, muscle stiffness and spasticity). Adverse effects most frequently reported such as fatigue and dizziness were mild to moderate in severity and generally well tolerated. This review adds further support that currently available cannabinoids are safe, modestly effective analgesics that provide a reasonable therapeutic option in the management of chronic non-cancer pain.

**Keywords** Cannabinoids · Chronic non-cancer pain · Neuropathic pain · Systematic review · Marijuana

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<sup>2</sup> Departments of Anesthesia and Family Medicine, McGill University,

*“currently available cannabinoids are safe, modestly effective analgesics that provide a reasonable therapeutic option in the management of chronic non-cancer pain.”*

- M.E. Lynch & M.A. Ware; J Neuroimmune Pharmacology 2015

Research

Web exclusive

## Efficacy and adverse effects of medical marijuana for chronic noncancer pain

Systematic review of randomized controlled trials

Amol Deshpande MD MBA · Angela Mailis-Gagnon MSc MD FRCP · Nivan Zohairy MD PhD · Shehna Fatima Lakha

### Abstract

**Objective** To determine if medical marijuana provides pain relief for patients with chronic noncancer pain (CNCP) and to determine the therapeutic dose, adverse effects, and specific indications.

**Data sources** In April 2014, MEDLINE and EMBASE searches were conducted using the terms *chronic noncancer pain, smoked marijuana or cannabinoids, placebo and pain relief, or side effects or adverse events*.

**Study selection** An article was selected for inclusion if it evaluated the effect of smoked or vaporized cannabinoids (nonsynthetic) for CNCP; it was designed as a controlled study involving a comparison group, either concurrently or historically; and it was published in English in a peer-review journal. Outcome data on pain, function, dose, and adverse effects were collected, if available. All articles that were only available in abstract form were excluded.

**Synthesis** A total of 6 randomized controlled trials (N=226 patients) were included in this review; 5 of them assessed the use of medical marijuana in neuropathic pain as an adjunct to other concomitant analgesics including opioids and anticonvulsants. The 5 trials were considered to be of high quality; however, all of them had challenges with masking. Data could not be pooled owing to heterogeneity in delta-9-tetrahydrocannabinol potency by dried weight, differing frequency and duration of treatment, and variability in assessing outcomes. All experimental sessions in the studies were of short duration (maximum of 5 days) and reported statistically significant pain relief with nonserious side effects.

### EDITOR'S KEY POINTS

• Medical marijuana has been proposed as a potential treatment for use in pain management. However, there is still uncertainty about the specific indications, ideal doses, and adverse effects that are related to this substance when used for medical purposes.

*“There is evidence for the use of low-dose medical marijuana in refractory neuropathic pain in conjunction with traditional analgesics.”*

- A. Deshpande et al; CFP 2015

are common even with low-dose, short-term use of medical marijuana but they appear well tolerated. However, the long-term consequences of medical marijuana remain unknown.

This article has been peer reviewed.  
Can Fam Physician 2015;61:e372-81

Original Investigation

## Cannabinoids for Medical Use: A Systematic Review and Meta-analysis

Penny F. Whiting, PhD; Robert F. Wolff, MD; Sahar Deshpande, MSc; Marcello Di Nisio, PhD; Steven Duffy, PgD; Adrian V. Hernandez, MD, PhD; J. Christiaan Keurentjes, MD, PhD; Shona Lang, PhD; Kate Misso, MSc; Steve Ryder, MSc; Simone Schmidtkofer, MSc; Marie Westwood, PhD; Jos Kleijnen, MD, PhD

**IMPORTANCE** Cannabis and cannabinoid drugs are widely used to treat disease or alleviate symptoms, but their efficacy for specific indications is not clear.

**OBJECTIVE** To conduct a systematic review of the benefits and adverse events (AEs) of cannabinoids.

**DATA SOURCES** Twenty-eight databases from inception to April 2015.

### STUDY SELECTION

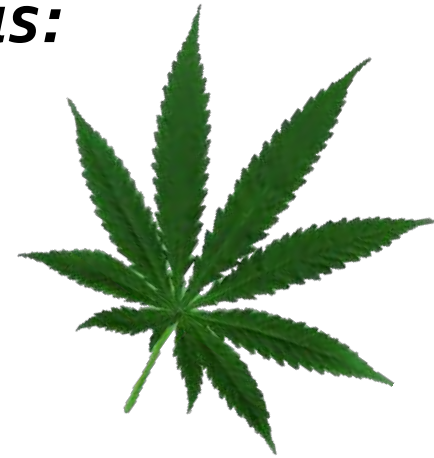
**RESULTS** A total of 79 trials (6462 participants) were included; 4 were judged at low risk of bias. Most trials showed improvement in symptoms associated with cannabinoids but these associations did not reach statistical significance in all trials. Compared with placebo, cannabinoids were associated with a greater average number of patients showing a complete response and vomiting response (47% vs 20%; odds ratio [OR], 3.82 [95% CI, 1.55-9.42]; 3 trials), reduction in pain (37% vs 31%; OR, 1.41 [95% CI, 0.99-2.00]; 8 trials), a greater average reduction in numerical rating scale pain assessment (on a 0-10-point scale; weighted mean difference [WMD], -0.46 [95% CI, -0.80 to -0.11]; 6 trials), and average reduction in the Ashworth spasticity scale (WMD, -0.12 [95% CI, -0.24 to 0.01]; 5 trials). There was an increased risk of short-term AEs with cannabinoids, including serious AEs. Common AEs included dizziness, dry mouth, nausea, fatigue, somnolence, euphoria, vomiting, disorientation, drowsiness, confusion, loss of balance, and hallucination.

**CONCLUSIONS AND RELEVANCE** There was moderate-quality evidence to support the use of cannabinoids for the treatment of chronic pain and spasticity. There was low-quality evidence suggesting that cannabinoids were associated with improvements in nausea and vomiting due to chemotherapy, weight gain in HIV infection, sleep disorders, and Tourette syndrome. Cannabinoids were associated with an increased risk of short-term AEs.

*There was moderate-quality evidence to support the use of cannabinoids for the treatment of chronic pain and spasticity.*  
- P.F. Whiting et al; JAMA 2015

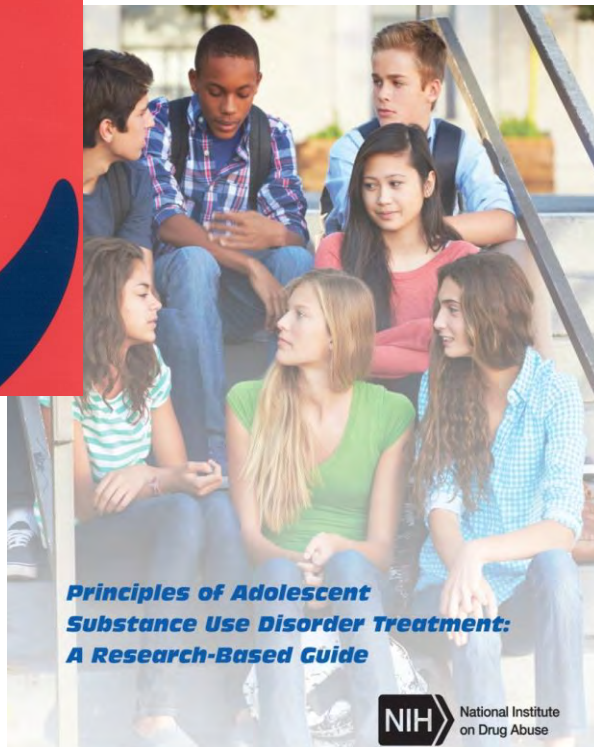
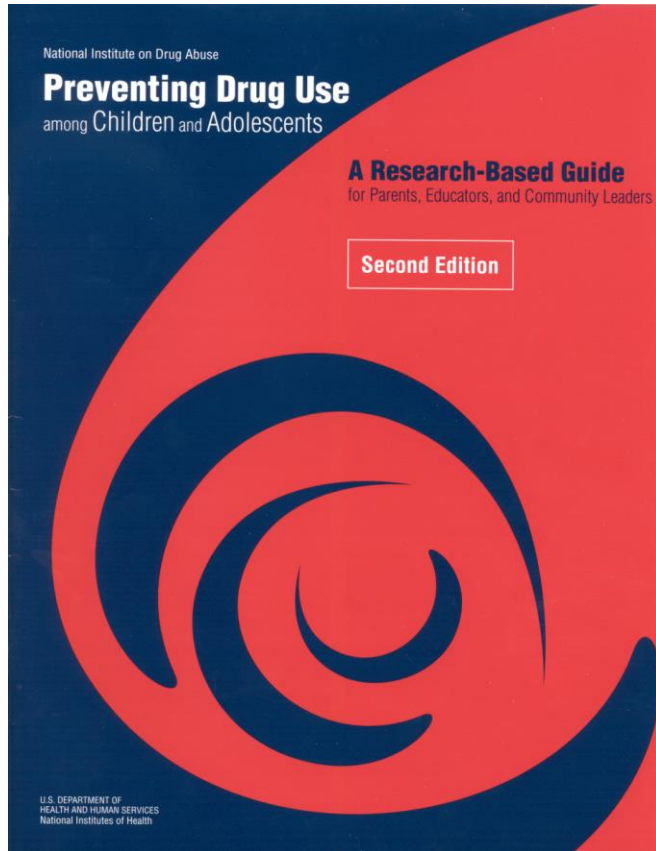
# Summary

- Marijuana is **most commonly used** illicit drug in U.S.
- Marijuana use generally **begins in adolescence**
- Use of marijuana can have a **wide range of effects on an individual's brain, body and behavior** including short and long term effects on such functions as:
  - ✓ Brain development
  - ✓ Memory and cognition
  - ✓ Motivational systems and reward
  - ✓ Addiction
  - ✓ Lung health
- Research on the impact of marijuana on the **developing adolescent brain** is important.
- **Medical** uses of marijuana are most likely from plant **cannabinoid constituents**





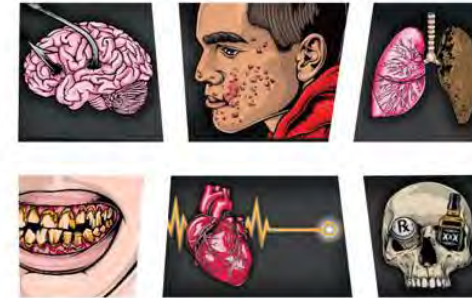
[www.drugabuse.gov](http://www.drugabuse.gov)



**Science = Solutions**

## **DRUGS + YOUR BODY:** **It Isn't Pretty**

- **Web Interactive**
- **[scholastic.com/  
drugsandyourbody\\_web](http://scholastic.com/drugsandyourbody_web)**



Web interactive

[Drugs + Your Body: It Isn't  
Pretty](http://scholastic.com/drugsandyourbody_web)

*Includes graphics, videos,  
quizzes and much more on the  
wide-ranging harmful effects  
of drugs on the brain and body.*